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The frequency of Celiac disease in primary Sjögren's syndrome

Primer Sjögren sendromunda Çölyak hastalığının sıklığı

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Abstract

Objective: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, affecting many organs. Celiac disease (CD), which causes inflammatory damage to the small intestine, develops as a result of the immunological response to gluten. The incidence of CD has increased in pSS. This research aims to investigate the frequency of CD in pSS.

Methods: This is a cross-sectional study conducted in a single-center between 2019 and 2020. A total of 90 patients diagnosed with pSS were questioned regarding CD symptoms. Laboratory tests and small bowel biopsies were requested from patients with suspected CD. Anti-gliadin immunoglobulin (Ig)A and IgG, anti-tissue transglutaminase (anti-TTG) IgA and IgG antibodies from celiac antibodies were evaluated using the ELISA method, and anti-endomysium IgA and IgG were evaluated by indirect immunofluorescence. Upper gastrointestinal endoscopy was performed in patients with CD symptoms and autoantibody positivity. The diagnosis of CD was made according to endoscopic biopsy results.

Results: The pSS patients comprised 98% females, with a mean age of 51.6±11.5 years. The rates of CD symptoms were as follows: 10% loss of appetite, 13.3% abdominal pain, 11.1% diarrhea, 18.9% constipation, 37.8% flatulence, and 2.2% weight loss. Anti-gliadin IgA positivity was determined in 6.7%, anti-gliadin IgG in 6.7%, anti-endomysium IgA in 2.2%, anti-endomysium IgG in 15.6%, and IgA in 1.1%. Gastroscopy was planned for 43 patients with suspected CD based on clinical and laboratory findings. CD was diagnosed in two patients before this study; subsequently, four more patients were diagnosed with CD.

Conclusion: The findings of this investigation revealed a 6.7% prevalence of CD in pSS. The diagnosis of CD in pSS was supported by histopathology. According to these findings, CD is more prevalent in pSS patients, and the risk of developing CD is higher than that in the general population.

Keywords: Sjögren's syndrome, Celiac disease, gluten

Öz

Amaç: Primer Sjögren sendromu (pSS), ekzokrin bezlerin lenfositik infiltrasyonu ile karakterize, birçok organı etkileyen sistemik, otoimmün bir hastalıktır. Glutene karşı gelişen immünolojik yanıt sonucu ortaya çıkan Çölyak hastalığı (ÇH), ince bağırsakta enflamatuvar hasara neden olur. ÇH'nin pSS'de insidansı artmıştır. Bu araştırmanın amacı, pSS'de ÇH sıklığını incelemektir.

Yöntem: Bu çalışma, 2019-2020 yılları arasında tek merkezde yürütülen kesitsel bir çalışmadır. pSS tanısı alan toplam 90 hasta, ÇH semptomları açısından sorgulandı. ÇH şüphesi olan hastalardan laboratuvar testleri ve ince bağırsak biyopsisi istendi. Çölyak antikorlarından anti-gliadin immünoglobulin (IgG), anti-doku transglutaminaz (TTG) (IgG) antikorları ELISA yöntemi ile ve anti-endomisyum IgA-IgG ise indirekt immünofloresan yöntemi ile değerlendirildi. ÇH semptomları ve otoantikor pozitifliği olan hastalara üst gastrointestinal sistem endoskopisi yapıldı. ÇH tanısı, endoskopik biyopsi sonuçlarına göre kondu.

Bulgular: pSS hastalarının %98'i kadın olup, ortalama yaşları 51,6±11,5 yıl idi. ÇH semptom oranları şu şekildedir; %10 iştah kaybı, %13,3 karın ağrısı, %11,1 ishal, %18,9 kabızlık, %37,8 gaz ve %2,2 kilo kaybı. Anti-gliadin IgA pozitifliği %6,7, anti-gliadin IgG %6,7, anti-endomisyum IgA %2,2, anti-endomisyum IgG %15,6 ve anti-TTG IgA %1,1 olarak saptandı. Klinik ve laboratuvar bulgularına göre ÇH şüphesi olan 43 hastaya gastroskopi planlandı. Bu çalışmadan önce iki hastada ÇH tanısı konmuştu, çalışmadan sonra ise 4 hastaya daha ÇH tanısı kondu.

Sonuç: Bu araştırmanın bulguları, pSS hastalarında %6,7 oranında ÇH prevalansı olduğunu ortaya koydu. pSS'te ÇH tanısı, histopatolojik bulgularla desteklendi. Bu bulgulara göre, ÇH pSS hastalarında daha yaygın olup, ÇH gelişme riski genel popülasyona göre daha yüksektir.

Anahtar Kelimeler: Sjögren sendromu, Çölyak hastalığı, gluten

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Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by lymphoplasmacytic infiltration of exocrine glands.[1] The disease affects many organs and systems.[2] In addition to gastrointestinal system findings such as dysphagia, pancreatic dysfunction, antral inflammation in the stomach, and autoimmune liver disease,[1] the frequency of Celiac disease (CD) has increased in pSS patients.[3,4]

An immune reaction to gluten and related proteins causes CD to manifest with inflammatory damage to the small intestine. Adult CD clinical symptoms can vary greatly. Gastrointestinal findings in patients may range from asymptomatic to malabsorption-related findings. Abdominal pain, diarrhea, dyspepsia, osteoporosis, dermatitis herpetiformis, infertility, and persistent anemia (due to iron, folic acid, or vitamin B12 deficiency) are common findings.[5] CD is categorized into three clinical forms -classical, atypical, or asymptomatic- depending on the presence of symptoms and/or extraintestinal findings. The classic form of CD presents with symptoms and signs of malabsorption. In approximately 50% of adult CD patients, gastrointestinal symptoms are non-specific.[6] Patients with atypical forms may have extraintestinal or gastrointestinal symptoms, such as stomach discomfort, constipation, vomiting, and distension. Hematological, endocrine, renal, rheumatological, and dermatological symptoms may also occur, which can result in a delayed CD diagnosis.[6]

Most autoimmune diseases, including type 1 diabetes mellitus, autoimmune thyroid disease, and Sjögren's syndrome (SS), are more common in celiac sufferers compared to the general population.[6] Data on the incidence and prevalence of autoimmune diseases are limited. A population-based study[7] conducted in the UK observed a 22% increase in new diagnoses of autoimmune diseases between 2000 and 2019. A significant portion of this increase was attributed to patients who initially had one autoimmune disease and were subsequently diagnosed with a second. Notably, there was an increase in diagnoses of CD, Graves' disease, and SS.

Since the first study by Pittman and Holub,[8] several studies have explored the relationship between these two diseases.[3,4,9,10] These studies emphasize the increased frequency of CD in SS. The British Society for Rheumatology guidelines for managing adult and juvenile-onset SS[11] highlight the importance of the anti-tissue transglutaminase (anti-TTG) test used in the diagnosis of CD, citing data from some population-based studies,[12] including the findings of two studies.[3,4] Anti-TTG has also been recommended as a screening test after SS diagnosis to identify comorbidities and related autoimmune diseases in SS patients.

In light of all these data, considering that adult patients may be asymptomatic concerning CD, SS patients were included in this study. This study's objective was to investigate the frequency of CD in pSS patients monitored in our outpatient clinic.

Materials and Methods

This study is a cross-sectional study conducted in a single center between 2019 and 2020. Ninety pSS patients who fulfilled the classification criteria of the European-American Consensus Group[13] and were admitted to the rheumatology outpatient clinic between 2004 and 2020 were screened for CD symptoms, including abdominal pain, appetite loss, nausea, diarrhea, constipation, flatulence, and weight loss. The laboratory tests included anemia panel examinations, vitamin D levels, anti-TTG immunoglobulin (Ig)A and IgG, anti-endomysium IgA and IgG, and anti-gliadin IgA and IgG antibodies. Deamidated gliadin peptide antibodies (DGP) were not studied because they are not routine tests. Anti-gliadin IgA and IgG, and anti-TTG IgA and IgG antibodies were evaluated using the ELISA method (anti-TTG IgA cut-off >20 U/mL, anti-TTG IgG cut-off >1 U/mL, anti-gliadin IgA and IgG cut-off >25 U/mL). Anti-endomysium IgA and IgG were evaluated using indirect immunofluorescence, and the outcomes were reported as positive or negative. Upper gastrointestinal endoscopy was conducted in patients with pronounced CD symptoms, persistent anemia, and especially those with positive celiac antibodies. A small intestinal biopsy was taken to confirm the diagnosis of CD. All patients gave written informed consent to participate in the study. The characteristic histological changes linked to CD include crypt hyperplasia, flattening or deletion of villi (villus atrophy), and an increase in intraepithelial lymphocytes.[14] Patients were evaluated according to the diagnostic CD algorithms recommended by the American College of Gastroenterology.[15] The Kocaeli University Ethics Committee approved the study protocol (date: 19.04.2021, approval number: 2021/151).

Statistical Analysis

IBM SPSS software version 20.0 (IBM Corp., Armonk, NY, USA) was used to statistically analyze the study's data. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to determine if the data adhered to a normal distribution. Numerical variables were presented as mean ± standard deviation and median ± IR (min-max) values, and categorical variables as number (n) and percentage

(%). For numerical variables with a normal distribution, the Independent Samples t-test was used to compare group differences; for variables without a normal distribution, the Kruskal-Wallis and Mann-Whitney U tests were used. Factors impacting the relevant variable were identified using logistic regression analysis. Relationships between categorical variables were assessed using chi-square analysis. A p-value <0.05 was considered statistically significant for two-sided hypothesis testing.

Results

The laboratory, clinical, and demographic characteristics of individuals with pSS are presented in Table 1. The pSS patients comprised 98% females and 2% males, with a mean age of 51.6±11.5 years and mean disease duration of 7.3±4.1 years. The rheumatoid factor test was positive in 60% of patients, while antinuclear antibody, SS-A, and SS-B positivity rates were 90%, 61.1%, and 47.8%, respectively. Salivary gland biopsy was conducted in 81.1% of the participants, and 76.7% of these supported the diagnosis of pSS. In salivary gland scintigraphy, decreased uptake and excretion were detected in 70% of the patients. The clinical and demographic characteristics of pSS patients are presented in Table 1.

The patients were primarily questioned about CD symptoms. The clinical and laboratory findings related to CD are presented in Table 2. The presenting symptoms were as follows: Loss of appetite in 10%, nausea in 7.8%, abdominal pain in 13.3%, diarrhea in 11.1%, constipation in 18.9%, flatulence in 37.8%, and weight loss in 2.2% of the patients. Despite being affected by many parameters, 31.1% of patients had iron deficiency, 22.2% had folate deficiency, 36.7% had vitamin B12 deficiency, 88.8% had vitamin D deficiency, and 52.2% had osteoporosis. Leukopenia was determined in 25.6% of patients, and no patient had thrombocytopenia. The C3 level was low in 11.1% of patients, the C4 level was low in 3.3%, and 21.1% had hypergammaglobulinemia. IgA levels were normal in all patients. When CD antibodies were examined, anti-gliadin IgA positivity was found in 6.7% of patients, anti-gliadin IgG in 6.7%, anti-endomysium IgA in 2.2%, anti-endomysium IgG in 15.6%, and TTG IgA in 1.1%. Anti-TTG IgG was negative in all patients (Table 2).

Gastroscopy was performed for cases with suspected CD based on clinical and laboratory findings. Thus, gastroscopy data for 43 patients were obtained. According to gastroscopy, reflux was observed in 9.3% of patients, pangastritis in 16.3%, erythematous gastroduodenitis in 30.2%, erythematous antral gastritis in 37.2%, duodenitis in 4.7%, and atrophic gastritis in 2.3%. In the duodenal biopsy, intraepithelial lymphocytosis was detected in 41.9% of patients, blunting of villi in 16.3%, and crypt hyperplasia in 16.3%. *Helicobacter pylori* was detected in biopsy samples from 23.3% of patients. The gastric biopsy results showed chronic inflammation in 27.9% of patients, intestinal metaplasia in 9.3%, antral gastritis in 37.2%, and dysplastic changes in the stomach in 2.3%.

Following this stage, the clinical, laboratory, gastroscopy, and biopsy results of the patients were re-evaluated by

Table 1. Clinical and demographic features of patients with primary Sjögren's syndrome

Feature	n (%)
Gender	
Female	88 (97.8)
Male	2 (2.2)
Dry mouth	76 (84.4)
Dry eye	79 (87.8)
Arthritis	31 (34.4)
Parotitis	17 (18.9)
Vasculitis	4 (4.4)
Raynaud phenomenon	22 (24.4)
Neuropathy	6 (6.7)
Myositis	2 (2.2)
Lymphadenopathy	28 (31.1)
Interstitial lung disease	7 (7.8)
Nephrological involvement	6 (6.7)
Rheumatoid factor positivity	54 (60)
Antinuclear antibody positivity	81 (90)
Anti-SSA positivity	55 (61.1)
Anti-SSB positivity	43 (47.8)
Salivary gland biopsy positivity	56/73 (76.7)

Table 2. Clinical and laboratory findings of patients in terms of Celiac disease

Finding	n (%)
Loss of appetite	9 (10)
Nausea	7 (7.8)
Abdominal pain	12 (13.3)
Diarrhea	10 (11.1)
Constipation	17 (18.9)
Flatulence	34 (37.8)
Iron deficiency	28 (31.1)
Vitamin B12 deficiency	33 (36.7)
Folate deficiency	20 (22.2)
Vitamin D deficiency	80 (88.8)
Anti-gliadin IgA	6 (6.7)
Anti-gliadin IgG	6 (6.7)
Anti-endomysium IgA	2 (2.2)
Anti-endomysium IgG	14 (16)
Anti-TTG IgA	1 (1.1)
Anti-TTG IgG	-

Ig: Immunoglobulin, TTG: Anti-tissue transglutaminase

the gastroenterology department. Two patients had been diagnosed with CD before this study and had followed a gluten-free diet for many years. Based on the data obtained in the study, four more patients were diagnosed with CD. These patients have been following a gluten-free diet for approximately two years. A significant reduction in symptoms was observed in patients after starting a gluten-free diet.

When pSS patients with and without CD were compared, a statistically significant difference was observed regarding loss of appetite, flatulence, and arthritis. These results are presented in Table 3.

In the laboratory findings, statistically significant differences were observed in terms of iron deficiency and the presence of anti-endomysium IgG and anti-gliadin IgG. When gastroscopy and pathology biopsy results were evaluated, the presence of duodenitis, intraepithelial lymphocytosis, villus atrophy, and crypt hyperplasia were found to be significantly different between the groups (Table 4).

A significant correlation was also observed in the regression analysis of laboratory and clinical findings. In multivariate analysis, only loss of appetite and the presence of atrophic villi in duodenal biopsy were linked to the

Table 3. Comparison of clinical features of primary Sjögren's syndrome patients with and without Celiac disease

Feature	With CD (n=6)	Without CD (n=84)	p
Gender			
Female	6 (100)	82 (97.6)	1
Male	-	2 (2.4)	
Age* (mean ± SD)	49.7±5.6	51.7±11.9	0.457
Disease duration* (mean ± SD)	7.5 (5.3-11.5)	7 (4-9.9)	0.593
Disease onset age* (mean ± SD)	41.2±6.1	44.5±11.5	0.267
Dry mouth	6 (100)	70 (83.3)	0.585
Dry eye	6 (100)	73 (86.9)	1
Arthritis	5 (83.3)	26 (31)	0.017
Parotitis	1 (16.7)	16 (19)	1.000
Vasculitis	-	4 (4.8)	-
Neuropathy	-	6 (7.1)	-
Loss of appetite	4 (66.7)	5 (6)	0.001
Nausea	1 (16.7)	6 (7.1)	0.394
Diarrhea	2 (33.3)	8 (9.5)	0.131
Abdominal pain	2 (33.3)	10 (11.9)	0.189
Constipation	2 (33.3)	15 (17.9)	0.316
Flatulence	5 (83.3)	29 (34.5)	0.027
Weight loss	1 (16.7)	2 (2.4)	0.218

**CD: Celiac disease, years, SD: Standard deviation*

Table 4. Comparison of laboratory and gastroscopic histopathology results of primary Sjögren's syndrome patients with and without Celiac disease

Finding	With CD (n=6)	Without CD (n=84)	p
Anti-gliadin IgA	1 (16.7)	5 (6)	0.361
Anti-gliadin IgG	3 (50)	3 (3.6)	0.004
Anti-endomysium IgA	2 (33)	-	-
Anti-endomysium IgG	6 (100)	8 (9.5)	0.000
Anti-TTG IgA	1 (16.7)	0	-
Iron deficiency	5 (83.3)	23 (27.4)	0.010
Folate deficiency	3 (50)	17 (20.2)	0.121
Vitamin B12 deficiency	4 (66.7)	29 (34.5)	0.187
Vitamin D deficiency	6 (100)	74 (88.1)	1.000
Histopathological findings			
Duodenitis	7 (100)	13 (15.5)	0.000
Intraepithelial lymphocytosis	5 (83.3)	14 (16.7)	0.001
Atrophic villi	4 (66.7)	4 (4.8)	0.000
Crypt hyperplasia	3 (50)	4 (4.8)	0.005

CD: Celiac disease, Ig: Immunoglobulin, TTG: Anti-tissue transglutaminase

presence of CD in pSS patients. The regression analysis of the relationship between the presence of CD and clinical, laboratory, and pathological findings in pSS patients is presented in Table 5.

Discussion

SS affects many organs and systems,[2] and CD frequency is known to increase in SS. This study investigated CD frequency in pSS patients and demonstrated an increased incidence of CD in SS patients compared to healthy individuals.

In this study, the most prevalent gastrointestinal symptoms in pSS patients with CD were flatulence and loss of appetite. Although the frequency of bloating was observed at different rates (46-73%) in various studies,[16,17] it was a prominent symptom in most CD patients in this study (83.3%). Loss of appetite has low sensitivity in diagnosing CD;[18] however, a significant correlation was observed between CD diagnosis and loss of appetite in this study. Abdominal pain, nausea, and diarrhea were less common symptoms. Anemia, the most frequent extraintestinal finding in CD, is seen in 20% of cases.[19] It can be due to iron, B12, or folate deficiency. The prevalence of iron deficiency anemia in CD varies between 3% and 5%. In this study, this rate was found to be quite high, possibly because the patient group primarily comprised females, and iron loss could be due to the menstrual cycle. Anemia and iron deficiency have been shown to improve with a gluten-free diet. Iron and folate deficiencies were higher in CD participants compared to non-CD participants. Anemia parameters improved in 85% of participants on a gluten-free diet, and iron therapy was also given to patients with poly-hypermenorrhea.

CD is an enteropathy triggered by gluten and associated with various autoantibodies. Both humoral and cellular immune responses play a role in CD. CD-specific antibodies include endomysial antibodies (EMA), DGP, and autoantibodies against transglutaminase 2.[20-22]

In CD diagnosis, both TTG and EMA tests have high specificity and sensitivity.[23] In this study, anti-TTG IgA and endomysium IgA were not detected in any pSS patients without CD. Anti-TTG IgA positivity was low in CD patients in this study; however, anti-endomysium IgG was positive in all CD patients. Although anti-gliadin antibodies have low specificity and sensitivity and are not used in diagnosis, anti-gliadin IgG was observed at a high rate in individuals with CD. DGP were not studied because this is not a routinely performed test.

The gold standard for diagnosing CD remains a small intestinal biopsy. Typical findings in endoscopic distal duodenal biopsies in CD include increased intraepithelial lymphocytes, crypt hyperplasia, and flattening or deletion of villi (villus atrophy).[14] Histopathological classifications, such as the Marsh-Oberhuber classification,[6,14] are used to grade intestinal mucosal lesions in CD. However, none of the histopathological findings listed above are pathognomonic for CD. Therefore, histopathological findings may need to be evaluated alongside serological and clinical findings, and genetic testing may be required for confirmation when necessary. In this study, all pSS patients with CD exhibited duodenitis, and CD-specific histopathological findings were identified in the biopsies. Regression analysis in this study revealed a significant correlation between these histopathological findings and CD diagnosis.

Previous studies show that CD frequency in pSS patients varies between 4.5% and 15%.[3,4,9,10] In a study by Iltanen et al.,[9] although the sample size was small, CD prevalence was found to be quite high in pSS patients. Histopathological data and positive celiac antibodies (anti-gliadin IgA and anti-endomysium IgA) were high in these patients.[9] Szodoray et al.[3] reported CD prevalence in pSS patients as 4.5%, with diagnosis confirmed by serology and histopathology. According to that study, SS patients with CD were younger than those without CD. In another study, the prevalence of CD in pSS patients was 7.06%, with the majority (24 out of 25) diagnosed with CD before the study, confirmed with an intestinal biopsy. It was also noted that pSS patients with CD were younger than those without CD and that CD was diagnosed at a younger age.[10] However, no significant age

Table 5. Regression analysis of the relationship between the presence of CD and clinical, laboratory, and pathological findings in pSS patients

	Univariate			Multivariate		
	p	OR	95% CI	p	OR	95% CI
Flatulence	0.044	9.48	1.06-85.04			
Iron deficiency	0.021	13.26	1.47-119.67			
Arthritis	0.031	11.15	1.24-100.29			
Loss of appetite	0.000	31.6	4.62-216.2	0.009	28.3	2.4-347.5
Intraepithelial lymphocytosis	0.005	25	2.70-230.73			
Atrophic villi	0.000	26.3	5.56-287.45	0.005	35.9	2.9-441.5
Crypt hyperplasia	0.002	20	3.02-132.29			

CD: Celiac disease, CI: Confidence interval, OR: Odds ratio, pSS: Primary Sjögren's syndrome

difference between the groups was observed in the present study.

The current study found the CD prevalence in pSS patients to be 6.7%. CD diagnosis in pSS patients was confirmed by histopathology. According to 2018 Ministry of Health public health data, CD prevalence in Türkiye is 1%.[24] Thus, the study suggests that CD prevalence in pSS patients is high, with an increased risk for CD compared to the general population.

Arthralgia and arthritis can be observed in CD patients. CD-associated arthritis was once thought to be rare, with a reported frequency between 0-26%. Non-erosive oligoarticular involvement occurs in peripheral large joints and is not associated with spondyloarthropathy or sacroiliitis.[25] Intermittent, non-erosive symmetrical inflammatory polyarthritis occurs in 30% of SS patients, particularly affecting the fingers, wrists, and ankles.[26] In this study, arthritis incidence in patients with CD was significantly higher than in the non-Celiac group. The arthritis pattern in CD patients in this study was symmetrical polyarthritis (60%) and an oligoarticular pattern (40%). None of the patients had a diagnosis of spondylitis.

Advanced complications of CD, such as collagenous sprue, ulcerative jejunoileitis, and enteropathy-associated T-cell intestinal lymphoma (EITCL), can occur at advanced stages of CD. EITCL is the most serious CD complication, with a poor prognosis.[27] Thus, it is crucial for patients to maintain a gluten-free diet and receive regular follow-ups after diagnosis.

Study Limitations

Study limitations include the small sample size and the low rate of anti-TTG antibodies, which have high sensitivity and specificity in diagnosis. The lack of both a patient control group and a healthy control group is another limitation. The use of anti-gliadin antibodies, which have low specificity, is also a limitation. A study strength is that patients were evaluated through detailed anamnesis, laboratory testing, gastroscopy, and histopathological examination for CD diagnosis.

Conclusion

The results of this study showed that CD prevalence is increased in patients with pSS. Therefore, CD should especially be considered in patients with treatment-resistant anemia, and a thorough gastrointestinal investigation with antibody screening and endoscopic examination is recommended. Patients should be monitored for malabsorption syndromes, anemia, and potential lymphoma development and managed with an appropriate diet.

Ethics

Ethics Committee Approval: The Kocaeli University Ethics Committee approved the study protocol (date: 19.04.2021, approval number: 2021/151).

Informed Consent: All patients gave written informed consent to participate in the study.

*Preliminary results of this study was presented as an oral presentation at the XX. National Rheumatology Congress (16-20 October 2019, Antalya SS-18).

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ö., Concept: Ö.Ö.I., M.Ö., D.T.K., Design: Ö.Ö.I., M.Ö., S.T., Data Collection or Processing: Ö.Ö.I., D.T.K., S.T., Analysis or Interpretation: Ö.Ö.I., A.Y., A.Ç., Literature Search: Ö.Ö.I., M.Ö., D.T.K., A.Y., Writing: Ö.Ö.I., D.T.K.

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